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Relationship between thyroid function tests and mortality in severe Covid-19 pneumonia cases admitted to the intensive care unit

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Abstract

Aim: In severe COVID-19 infection, most organs are affected, including the thyroid gland. A decrease in thyroid functions can be seen in relation to the severity of the disease. We aimed to retrospectively analyze the relationship between thyroid function tests and mortality in patients admitted to the intensive care unit (ICU) with severe COVID-19 pneumonia.

Material and Methods: The study was performed retrospectively on 46 adult patients admitted to the intensive care unit with severe COVID-19 pneumonia. Demographic, clinical, laboratory data were recorded. Patients were grouped into two according to mortality. Laboratory data were compared between groups. Additionally, the correlation of free triiodothyronine (fT3), free thyroxine (fT4), and thyrotropin (TSH) with infection parameters was investigated.

Results: At the time of ICU admission, fT3 levels below the normal range were present in 91.3%, fT4 levels were below normal in 39.13%, and TSH levels were below normal in 52.17% of the study patients. There was a positive correlation between fT4 and CRP ($r=0.315$, $p<0.05$), while there were no significant correlations between other parameters. TSH, fT3, or fT4 did not differ between patients with and without mortality. Partial arterial oxygen pressure/fraction of inspired oxygen was lower in patients with mortality ($p=0.015$).

Discussion: Low thyroid hormone levels and TSH are common occurrences in patients admitted to the ICU with severe COVID-19 pneumonia. No relationship could be shown between low thyroid function test levels and mortality in patients with severe COVID-19 pneumonia.

Keywords

COVID-19, Thyroid Function Tests, Thyroid Hormones, SARS-CoV-2, Intensive Care Units

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Introduction

The novel coronavirus infection (COVID-19) has a plethora of effects on the organ systems and can lead to severe respiratory insufficiency following pneumonia. Similar to other organs, the thyroid gland and its functions are affected during the COVID-19 infection. Among patients with COVID-19 infection, hypothyroidism is reported at a rate of 6.7%. A quarter of hypothyroidism cases in these patients are attributed to autoimmune thyroiditis, while 66% are attributed to central hypothyroidism due to corticotroph deficiency that has been shown in long-term follow-up to be transient [1]. Thyroid stimulating hormone (thyrotropin, TSH) levels are lower in severe COVID-19 patients, both during the initial course of the disease and during the recovery period [2]. The pituitary-adrenal axis is disrupted directly by viral infection of pituitary cells and indirectly by the proinflammatory cytokines [1].

Besides thyroid diseases, abnormal levels of thyroid hormones are seen in severe infection, hepatic or renal failure, malignancies, and severe malnutrition. These are collectively referred to as non-thyroidal illness (NTI) or euthyroid sick syndrome [2,3]. NTI is characterized by low plasma triiodothyronine (T3), low or normal plasma thyroxine (T4), and low or normal TSH levels. COVID-19 pneumonia patients differ from non-COVID pneumonia cases in that severe COVID-19 patients have lower serum TSH levels [2,4]. The decrease in TSH and T3 in COVID-19 patients is positively correlated with the severity of infection and the levels of interleukin-6 (IL-6), which increase with associated cytokine storm [1,2]. Based on these reports, serum TSH and thyroid hormone changes may be important markers in the course of COVID-19 disease. In this study, we aimed to investigate the relationship between thyroid function tests and mortality in patients admitted to the ICU with COVID-19 pneumonia.

Material and Methods

Following the local ethics committee (FSM EAH KAEK 2021/13) and the Ministry of Health approval, the study was conducted retrospectively in a single center. Data of 46 patients aged >18 admitted to the ICU between April 2020 - March 2021 with COVID-19 pneumonia confirmed with reverse-transcriptase polymerase chain reaction (RT-PCR) tests were collected and analyzed. RT-PCR specimens for COVID-19 testing were collected with nasopharyngeal swabs. Patients aged <18, with negative COVID-19 tests, known thyroid dysfunction, or under treatment for thyroid diseases, or who received treatment with steroids prior to ICU admission were excluded. The presence of at least one of the following criteria, together with unilateral or bilateral ground-glass images on lung computed tomography (CT), while classifying patients for severe COVID-19 pneumonia was used for inclusion: respiratory rate ≥30 breaths/minute, peripheral oxygen saturation (spO2) ≤93%, partial arterial oxygen pressure/fraction of inspired oxygen ratio (PaO2/FiO2) ≤ 300 mmHg, or need for high-flow oxygen or mechanical ventilation.

Demographic parameters [age, gender, comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores], clinical data [lung CT reports prior to ICU admission, symptoms at admission, peak heart rate (HR), blood pressure (BP), SpO2], ICU data [invasive mechanical ventilation (IMV) requirement, IMV duration, mortality], laboratory results at the time of ICU admission [fT3, fT4, TSH, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase (LDH), ferritin, interleukin-6 (IL-6), D-Dimer, PaO2/FiO2] were recorded. Fever was defined as body temperature ≥ 38 C^0, tachycardia as HR ≥ 100 beats/min, hypertension as systolic blood pressure ≥ 140 mmHg, and hypotension as systolic blood pressure < 90 mmHg. Neurological worsening was defined as an acute decrease in ≥ 2 points in the Glasgow Coma Scale score. Patients received IMV when hypoxia (SpO2 ≤ 92% or PaO2 < 60 mmHg), tachypnea (respiratory rate ≥ 30/min), and dyspnea persisted with clinical deterioration, hemodynamic instability, or worsening consciousness despite oxygen via reservoir mask, high flow nasal cannula, or non-invasive mechanical ventilation.

Patients were grouped into two according to mortality. Recorded data were compared between groups to investigate their relationship with mortality. The correlation of fT3, fT4, and TSH at the time of ICU admission with NLR, CRP, PCT, and IL-6 that represent the severity of infection were also investigated [5].

Statistical Analysis:

Statistical analysis was performed using IBM SPSS Version 26.0 (IBM Corp, 2019, Armonk NY). Categorical data are given in numbers and percentages, while continuous data are given as mean ± standard deviation or median (minimum-maximum). The Kolmogorov-Smirnov test was applied to test the normality of continuous variables. The Mann-Whitney U test was performed as continuous variables did not show a normal distribution. The correlation of thyroid hormones with infectious parameters was tested using Spearman's Rho Correlation. Statistical significance was set at $p<0.05$.

Results

A total of 46 patients admitted to the ICU with severe COVID-19 infection were retrospectively analyzed. None of the patients had any missing data among the parameters included in the analysis. The demographic parameters, symptoms, clinical findings at ICU admission, ICU outcomes, and laboratory parameters data are presented in Table 1 and Table 2.

At the time of ICU admission, relative to the normal ranges of laboratory, 91.3% of the patients had low fT3 (isolated low fT3 in 8, low fT3 and TSH in 16, low fT3 and fT4 in 8, low fT3, fT4, and TSH in 6, low fT3, fT4 with high TSH in 4 patients), and 39.13% had low fT4. Higher than normal fT3 or fT4 was not observed in any of the patients; 52.17% of the patients had low TSH and 8.7% had high TSH levels. In only two patients (4.34%), fT3, fT4, and TSH were within the normal ranges (data are not presented in the Tables). Laboratory results at the time of ICU admission were compared between patients with and without mortality. PaO2/FiO2 was significantly lower in patients with mortality. fT3, fT4, and TSH did not differ significantly between the groups (Table 3).

The correlation of fT3, fT4, and TSH with NLR, CRP, PCT, and IL-6 was investigated. There was a significant positive correlation between fT4 and CRP ($r=0.315$; $p<0.05$), while other

parameters were not found to be correlated.

Discussion

In our study, we investigated the relationship of thyroid hormones and thyroid stimulating hormone levels with mortality in patients who required ICU treatment due to severe COVID-19 pneumonia. In 95.6% of the study patients, at least one thyroid function test was outside of the normal range at the time of ICU admission. The most frequent thyroid dysfunction was low fT3 (91.3%), followed by low TSH (52.17%). In patients with mortality, thyroid hormone and thyroid stimulating hormone levels were lower than in patients without mortality albeit insignificantly. Among thyroid hormone levels at the time of ICU admission, only fT4 and CRP were positively correlated.

Studies have shown that there is a decrease in T3 levels in the acute period of critically ill patients, mainly due to the decrease in the conversion of T4 to T3 in peripheral tissues. In this period, short-term increases in TSH and T4 can also be observed. In the long-term critical illness period, central suppression of the thyroid axis may cause a decrease in T3, T4 and TSH concentrations [6,7]. Wang et al. have shown that in the acute phase of the SARS-CoV infection the thyroid functions are disrupted and in the majority of the patients a decrease in T3, T4, and TSH is observed [8]. They have also shown a correlation between disease severity and a decrease in fT3. Chen et al. have demonstrated a decrease in total T3 and TSH concentrations in COVID-19 pneumonia patients compared to their control group or patients with pneumonia of other causes [2]. Zou et al. have reported a 27.52% rate of NTI in COVID-19 patients and a higher risk of severe disease in patients with NTI [9]. Our study patients were admitted to the ICU with severe COVID-19 pneumonia and respiratory insufficiency. Most of our patients had low fT3 levels and most of these cases also had accompanying low TSH levels. We believe the thyroid dysfunction in our patients resulted from NTI arising from their severe acute infection.

Boelen et al. reported that the changes in thyroid hormone levels correlate with the severity of the disease resulting in NTI and that thyroid dysfunction recovered after treatment of the primary disease [10]. Chen at al. have shown that thyroid dysfunction, especially the decrease in T3, is more evident in patients with mortality [11]. Khoo et al. did not find a difference in TSH levels between patients with and without mortality, but slightly higher levels of fT4. Neither fT4 nor TSH was associated with mortality in their study [12]. C-reactive protein is accepted as a risk factor that correlated with disease severity in COVID-19 infections [13]. Zou et al. have found higher CRP, erythrocyte sedimentation rate, and procalcitonin in patients with NTI. In their patients, NTI was associated with inflammatory parameters of disease severity, however, did not affect mechanical ventilation requirement, time to discharge, or mortality [9]. In contrast, Muller et al. reported significantly higher CRP and free thyroxin levels in COVID-19 patients with mortality when compared to patients who survived. [14]. In our study, only fT4 and CRP were correlated among thyroid function tests and infectious parameters at the time of ICU admission. Free T3 and TSH levels were not correlated with infectious parameters. Although not statistically significant, we observed lower median fT3, fT4, and TSH levels in patients with mortality, while no association could be made between thyroid function tests and mortality. Of the parameters associated with disease severity, only PO2/FiO2 was associated with mortality.

Our study has certain limitations. Our study design did not include a control group, therefore, we could not make a comparison with healthy individuals or patients with non-COVID-19 pneumonia. Another limitation is that prior thyroid disease was questioned only with patient history and was not confirmed with radiological imaging when excluding patients.

Table 1. Demographics, clinical characteristics, and outcomes of ICU patients

	Median (min-max)	Mean ± SD
	n=46	n=46
Age	70.5 (38-94)	70.00± 14.74
Gender (Male/Female) n (%)	25/21 (54.3/45.7)	
APACHE II	18 (6-38)	19.46± 8.11
Any comorbidity n (%)	38 (82.6)	
≥ 2 Comorbidities n (%)	25 (54.3)	
Symptoms and Findings; n (%)		
Dyspnea	46 (100)	
Fever	4 (8.7)	
Chest Pain	4 (8.7)	
Diarrhea	6 (13)	
Neurological Worsening	16 (34.8)	
Tachycardia	39 (84.8)	
Hypotension (SBP < 90 mmHg)	8 (17.4)	
Hypertension (SBP > 140 mmHg)	11 (23.9)	
Lung CT Findings; n (%)		
Bilateral GGO	7 (15.2)	
Unilateral GGO	39 (84.8)	
IMV requirement n (%)	44 (95.7)	
IMV duration (days)	11 (0-69)	15.80± 14.38
ICU stay (days)	12 (1-69)	17.33± 14.70
Mortality n (%)	38 (82.6)	

APACHE II: Acute Physiology and Chronic Health Evaluation II, CT: Computed tomography, GGO: Ground glass opacity, IMV: Invasive mechanical ventilation, ICU: Intensive care unit, SBP: Systolic Blood Pressure

Table 2. Laboratory data of patients during admission to intensive care unit

Parameter	Nomal Range	All Patients (n=46)	
		Median (min-max)	Mean ± SD
fT3 ng/L	2,04-4,4	1.32 (0.88-2.42)	1,39±0.41
fT4 ng/dl	0,93-1,7	1,0 (0.40-1.83)	1.02±0.32
TSH mIU/L	0,54-4,31	0.48 (0.04-16.80)	1.61±3,49
LYM (103/mm3)	1,0-4,8	0.60 (0.20-2,0)	0.79±0.44
NLR	0,7-2,5	14,8 (2,0- 83,0)	21.99±18,23
CRP (mg/L)	0-5	24,60 (1.52- 307)	57,88±71,06
PCT (µg/L)	0-0.05	0.42 (0.05-20.9)	1,40± 3.45
LDH (U/L)	50-150	464,0 (142-936)	478,83 ±218,92
Ferritin (µg/L)	30-400	750,85 (38.7- 2990)	1046,86±777,55
IL-6 (pg/ml)	0-7	45.0 (4.30- 4056)	294,16±686,97
D-dimer (µg /mL)	0,00-0,50	2,59 (0.31-32)	4,51±6,32
PO2/fO2	>300	74(55-300)	93,65± 56,27

fT3: free triiodothyronine, fT4: free thyroxine, TSH: Thyroid stimulating hormone, LYM: Lymphocytes, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, PCT: Procalcitonin, LDH: Lactate dehydrogenase, IL-6: Interleukin-6, PaO2/FiO2: Partial arterial oxygen pressure/Fraction of inspired oxygen.

Table 3. Comparison of laboratory parameters according to mortality

Parameter	Alive (n=8)		Mortality (n=38)		p
	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	
fT3 ng/L	1.66 (0.92-2.30)	1.60±0.42	1.28 (0.88-2.42)	1.35±0.40	0.098
fT4 ng/dl	1.03 (0.52-1.48)	0.98±0.28	0.98 (0.40-1.83)	1.03±0.32	0.805
TSH mIU/L	0.89 (0.11-16.06)	2.63±5.45	0.44 (0.04-16.80)	1.39±2.99	0.653
LYM (103/mm3)	0.80 (0.60-1.70)	0.96±0.43	0.60 (0.20-2)	0.75±0.44	0.188
NLR	11.10 (6.29- 38.83)	15.66±12.23	15.70 (2- 83)	23.32±19.12	0.151
CRP (mg/L)	14.01 (3.67- 59.44)	22.37±21.25	33.28 (1.52- 307)	65.35±75.671	0.072
PCT (µg/L)	0.23 (0.05- 0.37)	0.37± 0.44	0.45 (0.05-20.9)	1.62± 3.76	0.082
LDH (U/L)	336 (208-936)	434.63±254.30	494.50 (142-895)	488.13±213.41	0.524
Ferritin (µg/L)	616.35 (119.5-1847)	810.02±622.67	780 (38.70- 2990)	1096.72±804.54	0.338
IL-6 (pg/ml)	33.50 (11.20-93)	41.77±26.97	49.00 (4.30- 4056)	347.29±746.43	0.277
D-dimer (µg /mL)	2.13 (0.51- 17.45)	3.79±5.62	3 (0.31-32)	4.66±6.51	0.487
PO2/fO2	100 (70-300)	122.88±81.50	70 (55-280)	87.50±48.69	0.015

Mann-Whitney U Test. fT3: free triiodothyronine, fT4: free thyroxine, TSH: Thyroid stimulating hormone, LYM: Lymphocytes, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, PCT: Procalcitonin, LDH: Lactate dehydrogenase, IL-6: Interleukin-6, PaO2/FiO2: Partial arterial oxygen pressure/Fraction of inspired oxygen.

Since mortality was considerably high in the studied patient population, our study groups were noticeably different in size. We regard our study as a guide for future studies that can be designed with a higher number of patients.

In conclusion, although low levels in thyroid function tests, especially fT3, are frequently encountered in patients admitted to the intensive care unit with severe COVID-19 pneumonia, we think that there is no direct relationship with mortality in our study.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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